Health technology
The study examined the use of first- versus second-generation antipsychotic drugs for patients with schizophrenia requiring a change of treatment because of poor response to previous therapy. The drugs included in the group of first-generation antipsychotics (FGAs) were chlorpromazine, flupentixol, haloperidol, loxapine, sulpiride, trifluoperazine and zuclopenthixol, plus depot antipsychotics (fluphenazine, zuclopenthixol, flupentixol and haloperidol decanoate). The drugs included in the group of second-generation antipsychotics (SGAs) were risperidone, olanzapine, amisulpride and quetiapine.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised patients with schizophrenia for whom a change in antipsychotic drug treatment was being considered because of intolerance or insufficient clinical improvement, and for whom a choice between an FGA and an SGA other than clozapine was relevant. The inclusion criteria were a DSM-IV diagnosis of schizophrenia, schizoaffective disorder or delusional disorder, age 18 to 65 years, and an interval of at least 1 month since the first onset of positive psychotic symptoms. The exclusion criteria were substance misuse or a medical disorder considered, clinically, to be the major cause of positive psychotic symptoms, or a history of neuroleptic malignant syndrome.

Setting
The setting was secondary care. The economic study was carried out in the UK.

Dates to which data relate
The clinical and economic data were derived from a study published in 2006. The costs were expressed using 2001/02 prices.

Link between effectiveness and cost data
The costing was performed prospectively on the same sample of patients as that used in the effectiveness analysis.

Study sample
The authors stated that the study had a 75% power to detect statistically significant differences between groups in the primary clinical outcome. Of the initial sample of 275 patients referred, 227 (82%) were included. There were 118 patients in the group using FGAs and 109 patients in the group using SGAs. The mean age was 40.5 (+/- 11.3) years in...
the FGA group and 40.9 (+/- 11.1) years in the SGA group. The proportions of male participants were 69% (FGA group) and 67% (SGA group), respectively.

**Study design**
This was a multi-centre, open, rater-blind, randomised controlled trial that was conducted in five centres in England, covering 14 NHS trusts. The length of follow-up was one year. Clinical data were available for 185 patients at the end of follow-up. Clinicians were asked to try to keep participating patients on the randomised medication for at least 12 weeks. The clinical outcomes were evaluated through patient questionnaires at 12, 24 and 52 weeks' follow-up. Both patients and physicians were aware of the treatment delivered. However, masked independent assessments were performed.

**Analysis of effectiveness**
The primary outcome measure was the score on the Quality of Life Scale (QLS). The EuroQol (EQ-5D) was also used for the current economic evaluation. The analysis of the clinical study was conducted on an intention to treat basis. At baseline, the two study groups were comparable with respect to their clinical and demographic characteristics. Missing values for patients who completed the scheduled follow-up but had missing observations were imputed using linear interpolation. Patients with one or more missing observations at the end of follow-up were treated as censored cases.

**Effectiveness results**
The utility values changed from 0.67 (+/- 0.29) at baseline to 0.78 (+/- 0.22) in the FGA group, and from 0.61 (+/- 0.33) to 0.75 (+/- 0.23) in the SGA group.

**Clinical conclusions**
The effectiveness analysis showed that health-related utility improved in both groups.

**Measure of benefits used in the economic analysis**
The summary benefit measure used was the quality-adjusted life-years (QALYs). These were estimated directly using the utility values derived from the clinical trial. Discounting was not performed because of the short-term time horizon.

**Direct costs**
The viewpoint of the analysis was that of the NHS, social support services and the patient. The health services included in the analysis were hospital inpatient and outpatient services, primary and community care, and prescribed medications. Details of the quantities of resources used, but not unit costs, were given. The total costs per category were presented at 12, 24 and 52 weeks. Resource consumption was based on data derived directly from the clinical trial using patient records and case-note reviews. Three methods of data collection were applied in order to derive the most accurate estimates of service use. The costs of the drugs, excluding dispensing and administration, came from the British National Formulary. Other costs were derived from the Personal Social Services Research Unit, as well as from other national sources. Discounting was not relevant given the 1-year timeframe of the analysis. The costs were standardised to 2001/02 prices using the health service price index when required.

**Statistical analysis of costs**
The total costs were presented as mean values with standard deviations.

**Indirect Costs**
Productivity costs were not included.
Currency
UK pounds sterling. 

Sensitivity analysis
The issue of uncertainty was addressed in a bootstrap analysis that generated cost-effectiveness acceptability curves. The net benefit was also calculated, which provided an estimate of the monetary value of a QALY at different values of societal willingness-to-pay. The incremental costs and QALYs were estimated by analysis of covariance, using a general linear model and covariates of baseline QLS score, utility, psychiatric hospital inpatient and outpatient costs prior to enrolment in the trial, and trial centre. Alternative sources of the costs for psychiatric services were considered in the sensitivity analysis. The impact of different imputation methods for missing values was also tested.

Estimated benefits used in the economic analysis
After one year of treatment, the expected QALYs were 0.74 (+/- 0.22) in the FGA group and 0.67 (+/- 0.25) in the SGA group.

When adjusted for covariates, the difference in QALYs was 0.04 (+/- 0.03) in favour of the FGA group.

Cost results
Over the 12-month follow-up period, the total costs were 18,858 (+/- 28,602) in the FGA group and 20,118 (+/- 25,348) in the SGA group. Thus, there was a trend towards lower costs in the FGA group.

The cost of antipsychotics represented only a small percentage of the overall costs (2% in the FGA group and 4% in the SGA group).

Hospitalisations represented the largest category of costs.

Synthesis of costs and benefits
The costs and benefits were not combined in a cost-utility ratio as switching to FGAs produced more QALYs at lower costs than switching to SGAs, which was a dominated strategy.

The sensitivity analysis indicated large standard errors associated with the difference in costs and QALYs, suggesting a high level of uncertainty. However, in all scenarios, FGAs dominated SGAs.

The cost-effectiveness acceptability curve showed that, at a willingness-to-pay of 35,000 per QALY gained, the probability that FGAs were cost-effective was 75%, with an associated net benefit of 1,752.

Overall, the probability that FGAs were cost-effective was between 54% (if decision-makers were willing to pay only 1 to gain one QALY) and 81% (if decision-makers were willing to pay up to 50,000 to gain one QALY).

Authors' conclusions
Conventional antipsychotics for the treatment of schizophrenia might be cost-effective in comparison with newer antipsychotics.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was clear. Newer antipsychotics were compared with conventional drugs. A list of drugs included in each category was provided. Clozapine was not considered. You should decide whether they are valid comparators in your own setting.
Validity of estimate of measure of effectiveness
The clinical evidence came from a clinical trial, which was appropriate for the study question. The use of assessment blinding and intention to treat analysis, and the multi-centre nature of the study enhances the internal validity of the analysis. However, neither the patients nor the physicians were blinded to treatment allocation, which could have introduced some bias, for example in the interpretation of side effects. Nevertheless, the authors pointed out that this should have favoured newer drugs. Further, the study was powered to detect statistically significant differences between the groups. The study groups were balanced at baseline, which improves the validity of the comparison. Statistical analyses were carried out to account for the potential impact of confounding factors, such as some baseline characteristics of the patients enrolled. Statistical techniques were used to take missing data into consideration. More details of the clinical trial might be found in the primary publication. A limitation of the clinical analysis was that, as the authors noted, there was insufficient information to determine whether the patients who participated in the trial were representative of eligible patients requiring a change in medication. Thus, caution will be required when considering the representativeness of this patient population.

Validity of estimate of measure of benefit
QALYs are an appropriate benefit measure of the impact of the interventions on patient health since the analysis focused on health-related quality of life, which is a relevant dimension of health for patients with schizophrenia. QALYs are also comparable with the benefits of other health care interventions. The authors stated that the EQ-5D is a validated instrument for people with schizophrenia.

Validity of estimate of costs
The analysis of the costs was consistent with the perspective adopted in the study. A breakdown of the cost items was given. Extensive details of resource quantities were provided, but the unit costs were not reported. The costs were derived from typical UK sources and the use of alternative sources was investigated in the sensitivity analysis. Statistical analyses were carried out to deal with the skewed distributions of the resources used. The price year was reported, thus facilitating reflation exercises in other time periods. The authors stated that the exclusion of costs of contacts with the criminal justice system, use of residential accommodation and informal care, might have resulted in an underestimation of total costs, although the amount of these items should have been limited over the trial observation period.

Other issues
The authors stated that their findings agreed with the conclusions of two UK-based economic modelling studies, although many studies suggest that SGAs may be cost-effective. The authors noted that the issue of missing clinical and economic data could have affected the robustness of the analysis, although the sensitivity analysis showed that the use of alternative imputation methods did not alter the results of the study. In addition, extensive statistical tests were carried out to address the issue of uncertainty. Another drawback of the analysis was the fact that the study had insufficient power to detect statistically significant differences in QALYs and costs.

Implications of the study
The study results do not support the widespread use of SGAs for the treatment of schizophrenia. The authors concluded that “further observational and pragmatic trials are required to identify cost-effective antipsychotic use, the determinants of costs and outcomes and the roles of first- and second-generation antipsychotic drugs in long-term management”.

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